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L8: Entry 10 of 24 File: USPT Aug 13, 2002

US-PAT-NO: 6432709
DOCUMENT-IDENTIFIER: US 6432709 B1

TITLE: Encapsidation cell lines and expression vectors for transcomplementation of defective retroviral vectors

DATE-ISSUED: August 13, 2002

INVENTOR-INFORMATION:

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US-CL-CURRENT: 435/350; 435/320.1, 435/325, 435/352, 435/363, 435/366, 435/455, 435/69.1

CLAIMS:

What is claimed is:

1. A cultured eukaryotic cell exhibiting the following properties: the cell is selected from a dog, the cell has a homogeneous morphology that is stable over time, the cell is not of tumor origin, the cell is selectable in a minimum culture medium lacking CO.sub.2, without prior transformation, and the cell exhibits accelerated kinetics, wherein the cell is suitable for packaging recombinant retroviral RNAs by transcomplementation.

2. The cell of claim 1, wherein the cell is a fetal or embryonic cell.

3. The cell of claim 1, wherein the cell is selected by a method comprising: a) culturing an eukaryotic cell on ISCOVE rich medium containing, in addition, 10% of fetal calf serum and 10% of horse serum; b) passing the cultured cell in DMEM medium containing 20% of fetal calf serum, recovering the selected cell, and culturing the cell for one month in a medium without CO.sub.2 ; c) selecting the cell exhibiting accelerated kinetics; d) passing the selected cell in DMEM medium containing 10% of fetal calf serum; e) passing the cell recovered in step d) in DMEM medium containing 10% of newborn calf serum; and f) recovering the cell selected at the end of step e).

4. The cell of claim 1, wherein the cell is a fetal dog cell DOGOM1 deposited at the Collection Nationale de Culture des Microorganismes (CNCM) on Nov. 30, 1994 under number I-1496.

5. The cell of claim 1, wherein the cell is a recombinant cell modified with nucleotide sequences coding for transcomplementing polypeptides and/or glycoproteins, the sequences being supplied by means of at least two vectors; and the cell packages recombinant retroviral RNAs by transcomplementation.

6. The cell of claim 5, wherein the cell is modified by transfection or by infection.

7. The cell of claim 5, wherein the nucleotide sequence of one of the vectors for transcomplementation, codes for envelope polypeptides and is modified by replacement of nucleotides by an arrangement of nucleotides coding for a sequence of a polypeptide or glycoprotein recognized specifically by a defined cell type, or by the addition of such an arrangement.

8. The cell of claim 5, wherein the recombinant cell is further transfected with a retroviral comprising a transgenic sequence, wherein said retroviral vector is the vector pFOCH29 deposited at the Collection Nationale de Culture des Microorganismes (CNCM) under No. I-1326, into which the transgenic sequence is inserted at a site which is non-essential for its replication.

9. The cell of claim 5, wherein the recombinant cell is modified with: a) a first expression vector for complementation with respect to the envelope, of a retroviral vector for the transfer and/or integration of a nucleotide sequence within the genome of a target cell, said first vector for complementation comprising a nucleotide sequence coding for envelope polypeptides and elements for regulation of the expression of the nucleotide sequence coding for envelope polypeptides; and b) a second expression vector for transcomplementation of GAG and POL polypeptides, of a retroviral vector for the transfer and/or integration of a nucleotide sequence within the genome of a target cell, said second vector for transcomplementation comprising: A) a gag nucleotide sequence coding for one or more nucleoprotein polypeptides from a Friend retrovirus; B) a pol nucleotide sequence coding of one or more polypeptides including a reverse transcriptase and an integrase from a Friend retrovirus; and C) transcription regulating signals controlling the expression of the gag and pol sequences, wherein the first and second expression vectors lack packaging signals.

10. The cell of claim 5, wherein the recombinant cell comprises: a) a gag nucleotide sequence coding for one or more nucleoprotein polypeptides from a Friend retrovirus; b) a pol nucleotide sequence coding for one or more reverse transcriptase and integrase polypeptides from a Friend retrovirus; c) transcription regulating signals controlling the expression of the gag and pol genes; d) an env nucleotide sequence coding for one or more amphotropic envelope polypeptides; and e) non-viral transcription regulating signals controlling the expression of the env sequence.

11. The cell of claim 5, wherein the cell comprises: a) a gag nucleotide sequence coding for one or more nucleoprotein polypeptides of a Friend retrovirus; b) a pol nucleotide sequence coding for one or more reverse transcriptase and integrase polypeptides of a Friend retrovirus; c) transcription regulator signals controlling the expression of the gag and pol genes; d) an env nucleotide sequence coding for one or more amphotropic envelope polypeptides; and e) non-viral transcription regulator signals controlling the expression of the env sequence.

12. The cell of claim 8, wherein the transgenic sequence is a nucleotide sequence coding for a gene intended for therapeutic purposes, or for an antisense nucleotide sequence, or for a dominant negative mutant of a gene or a sequence coding for a functional inhibitor of a gene, for a marker gene or for a sequence regulating a gene, or for a gene which adds a novel function to the target cell.

13. The cell of claim 9, wherein the gag and pol nucleotide sequences of said Friend retrovirus are from strain FB29, and wherein said gag and pol nucleotide sequences are under the control of the

transcription signals contained in the LTR sequence of the Friend retrovirus strain FB29, and wherein said cell comprises an env nucleotide sequence of a retrovirus of the spumavirus family, which is under the control of an inducible promoter.

14. The cell of claim 13, wherein the inducible promoter is a RAR.beta. promoter.

15. The cell of claim 9, wherein said transcription regulating signals comprise a non-viral promoter.

16. The cell of claim 15, wherein the promoter is an inducible promoter.

17. The cell of claim 16, wherein the inducible promoter is a RAR.beta. promoter.

18. The cell of claim 9, wherein the retroviral vector is a deletion mutant, a substitution mutant, or both, of vector pFOCH29, or is vector pFOCH29.

19. The cell of claim 18, wherein the vector is deleted within the LTR sequence.

20. The cell of claim 19, wherein the vector is .rho.FOCH29PL.

21. The cell of claim 11, wherein the transcription regulating signals controlling the expression of the gag and pol genes are non-viral signals.

22. The cell of claim 11, wherein the env nucleotide sequence encodes envelope 4070A of Moloney leukemia virus (Mo-MuLV).

23. The cell of claim 11, wherein non-viral transcription regulating signals controlling the expression of the env sequence comprise an inducible promoter or a conditional promoter.

24. The cell of claim 23, wherein the inducible promoter is a RAR-.beta. promoter.

25. An expression vector comprising: a) an env nucleotide sequence coding for one or more polypeptides from a retrovirus of the spumavirus family and permitting the packaging of retroviral RNAs; and b) transcription regulating signals controlling the expression of the env sequence; wherein the expression vector is used for transcomplementation of a retroviral vector, which transfers, integrates, or both, a nucleotide sequence within the genome of a target cell.

26. The vector of claim 25, wherein the env nucleotide sequence is from a HSVR spumavirus.

27. The vector of claim 25, wherein the transcription regulating signals comprise a non-viral promoter.

28. The vector of claim 25, wherein the transcription regulating signals are from the LTR sequence of Friend retrovirus.

29. The expression vector of claim 25, wherein the expression vector is an integrative vector.

30. The expression vector of claim 25, wherein the expression vector is used for transfection or infection of human cells in vitro.

31. The expression vector of claim 25, wherein the expression vector is an episomal vector.

32. The expression vector of claim 25, wherein the env nucleotide sequence codes for one or more truncated envelope polypeptides.

33. The expression vector of claim 25, wherein the env nucleotide sequence is modified by replacement of nucleotides by an arrangement of nucleotides coding for a polypeptide or glycoprotein recognized by a defined cell type, or by the addition of such an arrangement.

34. The vector of claim 25, wherein the nucleotide sequence of the expression vector for transcomplementation, coding for the envelope polypeptides, is modified.

35. The vector of claim 27, wherein the non-viral promoter is an inducible promoter.

36. The vector of claim 27, wherein the non-viral promoter is a conditional promoter.

37. The vector of claim 27, wherein the non-viral promoter is a RAR.beta. promoter of a retinoic acid .beta. receptor.

38. The vector of claim 34, wherein the modification comprises replacement of nucleotides by an arrangement of nucleotides coding for a polypeptide or glycoprotein recognized specifically by a defined cell type, or wherein the modification comprises addition of such an arrangement.

39. The expression vector of claim 30, wherein the human cells are endothelial muscle or stromal cells.

40. An expression vector comprising an env nucleotide sequence, coding for the envelope 4070A of Moloney leukemia virus (Mo-MuLV), said env nucleotide sequence being under the control of an inducible promoter.

41. An expression vector comprising an env nucleotide sequence, coding for envelope polypeptides from a retrovirus, said env nucleotide sequence being under the control of a RAR-.beta. promoter.

42. The expression vector of claim 40 or 41, wherein the env nucleotide sequence is modified.

43. The expression vector of claim 42, wherein the modification comprises replacement of nucleotides by an arrangement of nucleotides coding for a polypeptide or glycoprotein recognized specifically by a defined cell type, or wherein the modification comprises addition of such an arrangement.

44. The expression vector of claim 41, wherein the expression vector is an episomal vector.

45. An expression vector comprising: a) a gag nucleotide sequence coding for one or more nucleoprotein polypeptides of a Friend retrovirus; b) a pol nucleotide sequence coding for one or more pol polypeptides and including a reverse transcriptase protein and an integrase from a Friend retrovirus; and c) non-viral transcription regulating signals controlling the expression of the gag and pol sequences, wherein the vector is used for the transcomplementation of a retroviral vector,

that transfers and/or integrates a nucleotide sequence within the genome of a target cell.

46. The expression vector of claim 45, wherein the non-viral transcription regulating signals comprise an inducible promoter or a conditional promoter.

47. The expression vector of claim 46, wherein said inducible promoter is a RAR-.beta. promoter.

48. The expression vector of claim 25 or 45, wherein the expression vector lacks packaging signals.

49. The expression vector of claim 45, wherein the expression vector is an integrative vector.

50. The expression vector of claim 45, wherein the expression vector is used for transfection or infection of human cells in vitro.

51. The expression vector of claim 50, wherein the human cells are endothelial, muscle or stromal cells.

52. The expression vector of claim 45, wherein the expression vector is an episomal vector.

53. An expression vector comprising an env nucleotide sequence, coding for envelope polypeptides from a retrovirus, said env nucleotide sequence being under the control of the LTR sequence of Friend retrovirus.

54. An eukaryotic cell transformed by a vector of any one of claims 40, 41, 25, 45 and 53.

55. An eukaryotic cell transformed by a vector of claim 34.

56. An eukaryotic cell transformed by a vector of claim 42.

57. An expression vector comprising an env nucleotide sequence, coding for envelope polypeptides from a spumavirus, said env nucleotide sequence being under the control of an inducible promoter.

58. The expression vector of claim 57, wherein the spumavirus is HFV.

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L8: Entry 21 of 24 File: USPT Jan 12, 1999

DOCUMENT-IDENTIFIER: US 5858744 A
TITLE: Retroviral vector hybrids and the use thereof for gene transfer

Abstract Text (1):
Replication-defective retroviral vector hybrids which are characterized in that they contain a) the U5 region and/or tRNA primer binding site of MESV as the U5 region and/or tRNA primer binding site in the leader region and b) the U3 and R regions from a Friend murine leukaemia virus (F-MuLV) as the U3 and R regions in the 3'-LTR and which are particularly suitable for an effective gene transfer in haematopoietic stem cells.

Brief Summary Text (2):
The invention concerns retroviral vector hybrids and their use for gene transfer in particular for gene transfer into haematopoietic stem cells (ES).

Brief Summary Text (3):
Retroviral vectors with replication defects are at present a standard in gene transfer and gene therapy applications on cells of the human blood-forming system (A. D. Miller (1992) (1), R. C. Mulligan (1993) (2), R. Vile and S. J. Russell (1994) (3)). Their main advantages are:

Brief Summary Text (6):
the safety aspects of retroviral gene transfer are well researched; complications have so far not occurred in numerous applications on humans.

Brief Summary Text (7):
The most frequently cited advantage of retroviral vectors, their high gene transfer efficiency, only partly applies to applications on the blood-forming system. Only late maturing blood-forming precursor cells can preferably be infected with conventional vectors based on the Moloney murine sarcoma virus (MoMuSV); 30-95% of the precursor cells transduced with these vectors exhibit either no or an inadequate expression of the transferred genes due to primary silencing mechanisms (4); moreover after a longer residence period in vivo the retrovirally controlled gene expression is weakened in a high percentage of the initially expressing cells up to the point of non-function due to secondary silencing (Palmer et al. (1991) (5), Brenner et al. (1993) (6)).

Brief Summary Text (13):
b) contain the U3 and R regions from a Friend murine leukemia virus (F-MuLV) as U3 and R regions in 3'-LTR.

Brief Summary Text (15):
The vector hybrids according to the invention also preferably contain the LTR from a Friend murine leukemia virus (F-MuLV) as the 3'-LTR and thus also the U5 region from F-MuLV in addition to the U3 and R regions from MoMuLV and MESV.

Brief Summary Text (19):
More details of this and on the production of vectors, virus particles and helper cells are described in M. Kriegler, Gene Transfer and Expression, A Laboratory Manual, W. H. Freeman & Co., New York (1990), 47-55 and 161-164 (31). This

publication is a subject matter of the disclosure of the present application.

Brief Summary Text (25):
Retroviruses of the F-MuLV group are known to a person skilled in the art and are described for example in D. Linnemeyer et al. (1981) (7), J. Friel et al. (1990) (9), S. P. Clark and T. W. Mak (1982) (10), L. Wolff et al. (1985) (11), R. K. Bestwick et al. (1984) (12), W. Koch et al. (1984) (13) and A. Adachi et al. (1984) (14). A review is given in W. Ostertag et al. (1987) (15). The 3'-LTRs of malignant histiosarcoma virus (MHSV) (9), SFFVp Lilly-Steeves (10), SFFVa (11), Rauscher SFFV (12), F-MuLV c157 (13) and Friend-mink cell focus forming virus (F-MCFV FrNx (14), F-MCFV pFM548 (13)) are preferably used.

Brief Summary Text (27):
The advantages according to the invention are exhibited in transient transfections of reporter gene constructs in numerous representative cell lines of humans and mice. It has surprisingly turned out that U3 sequences of mouse retroviruses of the Friend murine leukemia virus (F-MuLV) family in combination with leader sequences (preferably tRNA binding site) of MESV enable an especially efficient gene expression in myeloid stem and precursor cells. The increase of the gene expression with the vector hybrids according to the invention is more than a power of ten compared to MoMUSV. This applies to relatively late precursor cells of the granulocytes, macrophages and erythrocytes as well as to the early multipotent precursors and even stem cells of the myeloid system. The vector hybrids according to the invention enable an efficient gene expression especially in the case of immature multipotent myeloid cells in which MoMuSV-LTR exhibits a pronounced primary silencing. The activity is also high in the lymphatic system as well as in fibroblasts.

Brief Summary Text (28):
An early isolate of the polycythaemia-inducing spleen focus forming virus (SFFVp (7)), is particularly preferred whose LTR sequence is described in SEQ ID NO:1 (bp 2654-3230) as well as the malignant histiosarcoma virus (MHSV (9), LTR SEQ ID NO:4, bp 1707-2324). In the U3 region of these viruses there is a high degree of sequence homology to other representatives of the Friend virus family such as SFFVp Lilly-Steeves (10), SFFVa (11), Rauscher SFFV (12), F-MuLV c 57 (13) and Friend-mink cell focus forming virus [F-MCFV FrNx (14), F-MCFV pFM548 (13)]. These and similar Friend-related retroviruses have a similar expression pattern as SFFVp and MHSV due to the sequence homology of the U3 regions.

Brief Summary Text (31):
In a further embodiment of the invention the retroviral vector hybrids can contain the U3 and R regions from MPSV as U3 and R regions in 3'-LTR. MPSV differs from MoMuSV and MoMuLV by point mutations in the LTR (21). In this case A(-381) is deleted and the following substitutions have been carried out C.fwdarw.T, -345; T.fwdarw.A, -326; T.fwdarw.A; -249 and A.fwdarw.C, -166 (numbering according to (21)). In this case the retroviral vector hybrid contains the U5 region and tRNA primer binding site of MESV in the leader region as the U5 region and tRNA primer binding site. It has turned out that such MPSV/MESV hybrid vectors (also called MPEV in the following) have considerable advantages compared to vectors based on MoMuLV and are of major importance for numerous applications in somatic gene therapy.

Brief Summary Text (32):
Any desired U3 and R regions can be used in 5'-LTR since after integration of the virus the U3 from the 3'-LTR is copied in the target cell also at the 5'-LTR position after completion of the retroviral life cycle and drives the gene expression. U3 and R regions are derived for example from MoMuLV or MoMuSV derivatives such as for example MPSV, PCMV and MESV. 5'-LTRs from F-MuLV are also suitable as the 5'-LTR.

Brief Summary Text (33):
The vector hybrids according to the invention exhibit a high tissue-specific expression after retroviral transduction of myeloid stem and precursor cells. These vectors therefore have the potential to considerably increase the gene transfer efficiency in myeloid stem and precursor cells compared to MoMuSV vectors. The vectors according to the invention additionally have the potential to be considerably less subject to silencing processes in myeloid cells than MoMuSV vectors. The high and possibly even persistent gene expression of these vectors in myeloid cells can form the basis for the successful application of numerous gene transfer protocols on the blood-forming system of humans. The constructs described in the examples are constructed in such a way that the cDNAs transferred by the vector can be replaced without difficulty by other genes.

Brief Summary Text (34):
The tissue specificity of the expression is suitable for abolishing the primary silencing in the myeloid system observed in the case of conventional MoMuSV vectors. This leads to a considerable increase in the functional gene transfer rates in myeloid cells. Since a high functional gene transfer rate is desired in most gene transfer/gene therapy applications on the myeloid system this is a generally usable advantage of the constructs according to the invention.

Brief Summary Text (35):
The Friend virus-related U3 regions were also selected in the myeloid system of the mouse for persistency of the gene expression in vivo. Secondary silencing occurred with these vectors to a much lower extent than with MoMuSV vectors. The exclusion of inhibitory leader sequences by substitution for MESV sequences is of additional advantage in this regard. This is of importance for all gene transfer/gene therapy applications in which a persistent (if possible life long) expression of the retrovirally transferred sequences is desired in the myeloid system (gene marker studies, correction of metabolic defects).

Brief Summary Text (37):
The production of a high virus titre in fibroblastoid packaging cell lines is a further important requirement for retroviral vectors which are intended to be used for gene transfer in myeloid cells. In the case of all the construct examples listed below the activity of the Friend-related U3 regions in fibroblastic retrovirus packaging cell lines is adequate to produce the required titre of 10.sup.5 to 10.sup.6 vector-transferring retroviral particles/ml cell culture supernatant.

Brief Summary Text (40):
b) the U3 and R regions from a Friend murine leukemia virus (F-MuLV) as the U3 and R regions in the 3'-LTR and

Brief Summary Text (42):
The LTR from F-MuLV is preferably used as the 3'-LTR which then contains the said U3 and R regions.

Brief Summary Text (45):
b) the U3 and R regions from a Friend murine leukemia virus (F-MuLV) as the U3 and R regions in the 3'-LTR.

Brief Summary Text (46):
This vector optionally contains one or several (up to three) exogenous genes which can be expressed in the eukaryotic cell. Mammalian cells preferably haematopoietic cells and especially haematopoietic stem cells are preferably used as eukaryotic cells. The LTR from F-MuLV is preferably used as the 3'-LTR which then contains the said U3 and R regions.

Brief Summary Text (48):

A further subject matter of the invention is a replication-defective infectious virus particle which contains a retroviral RNA as the genome wherein the genome contains a leader region from MESV which contains a packaging function and a tRNA binding site, and contains a heterologous gene for the virus which can be expressed in a eukaryotic cell and contains at the 3' end U3 and R from a Friend murine leukemia virus (F-MuLV) but no active gag, env and pol sequences.

Brief Summary Text (50):
A further subject matter of the invention is the use of a replication-defective retroviral vector hybrid according to the invention which contains the leader region of MESV as the leader region and the U3 and R regions from a Friend murine leukemia virus (F-MuLV) as the U3 and R regions in the 3'-LTR for the production of a pharmaceutical agent for ex vivo or in vivo gene therapy.

Brief Summary Text (53):
I. All somatic gene transfer/gene therapy methods in which myeloid stem cells and precursor cells are the target population for retroviral vectors.

Brief Summary Text (55):
Gene marker studies (1): Selectable marker genes such as neoR or shortened nerve growth factor receptor are transferred in order to monitor the fate of the labelled cell population in the organism under the conditions of the examined disease/therapy. The neoR vectors pSF1N and pMH1N which carry the neoR under the control of the SFFVp U3 and MHSV U3 (MESV leader) exhibit in comparison to neoR-transferring Maloney vectors a considerable increase in the functional gene transfer rate in the model system of the mouse stem cell line FDCPmix. They are suitable for neoR transfer in human myeloid stem cells.

Brief Summary Text (57):
Correction of metabolic diseases: In the case of monogenic hereditary diseases intact copies of the defective genes are introduced by means of retroviral gene transfer into myeloid stem cells. Applications are for example conceivable in the case of hereditary diseases whose gene defect has effects on the myeloid system (storage diseases such as the Hurler syndrome; M. Gaucher (29)):

Brief Summary Text (63):
Friend-related replication-competent viruses can in addition be used to produce forced passage mutants which also have an additional improvement of the infectiousness towards blood stem cells. Mutations in retroviral structural proteins of these viruses may be used to produce optimized packaging cell lines for gene transfer into myeloid cells. Mutations in cis regulatory sequences of these viruses may be used to further optimize retroviral vectors for blood stem cell gene transfer.

Brief Summary Text (64):
A further subject matter of the invention are ecotropic, xenotropic, amphotropic or polytropic retroviruses capable of replication containing the regulatory elements (leader region) of MESV and optionally MoMuLV or MoMuSV combined with the U3 and R regions from a Friend murine leukemia virus (F-MuLV) as U3 and R regions in the 3'-LTR, which as a result are capable of more efficiently infecting murine (in vivo and in vitro) or human (in vitro) precursor cells and to trigger mutations. The retroviruses preferably contain the LTR from F-MuLV as the 3'-LTR.

Brief Summary Text (72):
A further application is in experiments which have the goal of producing improved vector virus packaging lines, e.g. for gene therapy, which can produce viruses with a higher infection efficiency in precursor cells. In these cells there are several blocks which interfere with the retroviral infection/replication. The use of the constructs according to the invention has the advantage over replicatable wild-type MoMuLV or AM4070 that the transcriptional blocks are already removed. Improvements

in the infection efficiency can therefore be attributed to corresponding mutations in the viral proteins.

Detailed Description Text (7):
The backbone of these plasmids is based on the MESV vector R224 in which a major deletion had been carried out between the Xba1 cleavage site of the the 5'LTR and the Kpn1 cleavage site in the 3'LTR. The complementing sequences were inserted by means of three fragment ligations; base vectors pSF1, pSF2, pSF3 and pMH1 result (formation scheme and cloning strategy, FIG. 7, Table 1, sequences described in SEQ ID NO:1-4). The fragments used for the three fragment ligation are obtained from auxiliary constructs (see formation scheme, FIG. 6) in which simple modifications can be carried out in order to further optimize the vectors. It is also conceivable to substitute the SFFVp or MHSV U3 regions by analogous sequences of other Friend-related retroviruses or by the above-mentioned modifications of the leader in order to optimize the titre. The construct examples pSF 1N, pSF2N, pSF3N, pMh1N were obtained after insertion of the neoR cDNA (from R229). The construct examples carry polylinkers with singular restriction cleavage sites which can be used for the exchange of genes to be transferred. At these cleavage sites it is additionally possible to insert regulatory sequences for secondary gene expression that may be necessary such as the splice acceptor of SFFVp or the so-called internal ribosome entry site IRES (I. R. Ghattas et al. (1991) (26)).

Detailed Description Text (8):
The Friend-related regions cloned in the construct examples as U3 and R (in the 3'-LTR) are also copied at the 5'-LTR position after completion of a retroviral life cycle and then drive gene expression in the target cells. The construct examples contain all cis regulatory elements necessary for retroviral gene transfer and retroviral gene expression. Properties of SFFVp (or MHSV), MESV and MoMuSV are combined in these constructs. The point mutation of the start codon for the retroviral gag protein to form a stop codon (A. D. Miller and G. J. Rosman (1990) (27)) and the deletion of superfluous env sequences (27) are integrated as safety-relevant modifications in pSF1N, pSF2N, pSF3N, pMH1N.

Detailed Description Text (10):
Increasing the functional gene transfer rate in comparison to conventional Moloney vectors

Detailed Description Text (14):
K562 cells and TF1 cells were infected in an identical mixture with a Moloney-MDR1 vector (virus V-MDR resulting from the construct pVMDR) which is used in a clinical gene transfer protocol under the leadership of Prof. A. Deisseroth at the MD Anderson Cancer Center, Houston, Tex. As can be seen from Table 2 SF-MDR in the case of K562 leads to a 20-fold increase of the gene transfer rate compared to VMDR as measured by the number of colonies growing when cytostatic agents are administered (ca. 10-fold LD50 for K562).

Detailed Description Text (15):
The increase of the functional gene transfer rate in myeloid cells is an expression of the average increase of the gene expression rate in transduced cells. This is important in gene transfer applications whose success also depends on the level of gene expression (see example of application: protection of bone marrow in high-dose chemotherapy). If the cells are plated out with very high doses of cytostatic agents (ca. 20-fold LD50 for TF1) in the experiment described above (infection of human myeloid cells with SFMDR or V-MDR) only cells infected with SF-MDR are able to form colonies (Table 2).

Detailed Description Text (33):
(3) Vile R. and Russell S. J., Gene Therapy 1, 88-98 (1994)

Detailed Description Text (34):

(4) Lu M. et al., Human Gene Therapy 5, 203-208 (1994)

Detailed Description Text (58):
(28) Anderson W. F., Human Gene Therapy 5, 1-2 (1994)

Detailed Description Text (61):
(31) M. Kriegler, Gene Transfer and Expression, A Laboratory Manual, W. H. Freeman & Co., New York (1990), 47-55 and 161-164

Other Reference Publication (2):
Orkin et al., "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy", Dec. 7, 1995.

Other Reference Publication (11):
Valerio et al., Gene, vol. 84, 1989, pp. 419-427, "Retrovirus-mediated gene transfer into embryonal carcinoma and hemopoietic stem cells: expression from a hybrid long terminal repeat".

Other Reference Publication (13):
Couture et al., Human Gene Therapy, vol. 5, No. 6 (Jun.) 1994, pp. 667-677, "Retroviral vectors containing chimeric promoter/enhancer elements exhibit cell-type-specific gene expression".

Other Reference Publication (14):
Beck-Engeser et al., Human Gene Therapy, vol. 2, No. 1, 1991, pp. 61-70, "Retroviral vectors related to the Myeloproliferative sarcoma virus allow efficient expression in hematopoietic stem and . . . ".

Other Reference Publication (17):
Ostertag et al., 24th Annual Meeting of the International Society for Experimental Hematology, Aug. 27-31, 1995, Experimental Hematology (Charlottesville) 23 (8), (Aug. 30) 1995, 841, Abstract No. 344 "Novel and efficient retroviral vectors for somatic gene therapy and for stem cell protection.".

CLAIMS:

1. A retroviral vector hybrid comprising

a) a 5'-LTR-comprising at least one U5 region or tRNA primer binding site wherein the region or site is selected from the group consisting of the U5 region of MESV, the tRNA primer binding site of MESV, the U5 region of MoMuSV, and the tRNA primer binding site of MoMuSV, and

b) a 3'-LTR comprising the U3 and R regions from a Friend murine leukaemia virus (F-MuLV).

13. A process for the production of a retrovirally transduced eukaryotic cell which expresses an exogenous gene, said process comprising transducing a eukaryotic cell with a retroviral vector virus, which virus comprises

a) at least one U5 region or tRNA primer binding site wherein the region or site is selected from the group consisting of the U5 region of MESV, the tRNA primer binding site of MESV, the U5 region of MoMuSV, and the tRNA primer binding site of MoMuSV, and

b) a 3'-LTR comprising the U3 and R regions from a Friend murine leukaemia virus (F-MuLV).

16. An eukaryotic cell obtained by the process of transducing a eukaryotic cell with a retroviral vector virus comprising

a) at least one U5 region or tRNA primer binding site wherein the region or site is selected from the group consisting of the U5 region of MESV, the tRNA primer binding site of MESV, the U5 region of MoMuSV, and the tRNA primer binding site of MoMuSV, and

b) a 3'-LTR comprising the U3 and R regions from a Friend murine leukaemia virus (F-MuLV).

17. The cell of claim 16 wherein the F-MuLV is selected from the group consisting of malignant histiosarcoma virus (MHSV), SFFVp Lilly-Steeves, SFFVa, Rauscher SSFV, F-muLVc157 and Friend-mink cell focus forming virus.

20. A replication defective infectious virus particle comprising a retroviral RNA genome, wherein the genome comprises

a) at least one U5 region or tRNA primer binding site selected from the group consisting of the U5 region of MESV, the tRNA primer binding site of MESV, the U5 region of MoMuSV, and the tRNA primer binding site of MoMuSV, and

b) further comprises a packaging function, a gene which is heterologous to the virus and can be expressed in the eukaryotic cell, and U3 and R from a Friend murine leukaemia virus (F-MuLV), but

c) does not comprise active gag, env and pol sequences at the 3' end.

21. A process for the production of a replication defective infectious virus particle comprising

a) transfecting a eukaryotic helper cell which has the helper functions gag, env and pol with a vector hybrid comprising

i) at least one U5 region or tRNA primer binding site wherein the region or site is selected from the group consisting of the U5 region of MESV, the tRNA primer binding site of MESV, the U5 region of MoMuSV, and the tRNA primer binding site of MoMuSV, and

ii) a 3'-LTR comprising the U3 and R regions from a Friend murine leukaemia virus (F-MuLV),

b) producing the RNA corresponding to the DNA of the vector hybrid as the virus genome in the cell,

c) packaging the virus genome into the replication deficient empty virus envelopes formed in the cell, and

d) isolating the infectious virus particles which contain said virus genome.

22. The process of claim 21 wherein the F-MuLV is selected from the group consisting of malignant histiosarcoma virus (MHSV), SFFVp Lilly-Steeves, SFFVa, Rauscher SFFV, F-muLVc 157 and Friend-mink cell focus forming virus.

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End of Result Set

Generate Collection Print

L10: Entry 15 of 15 File: USPT Feb 23, 1993

DOCUMENT-IDENTIFIER: US 5188828 A
TITLE: Interleukin-6 to stimulate erythropoietin production

Brief Summary Text (17):
Recent studies (Koury, M. J., et al., J Cell Physiol 121:526-32 (1984)) have described the population of cells obtained from the spleens of mice during the acute disease caused by infection with the anemia-inducing strain of the Friend murine leukemia virus. In an elegant series of investigations, it was demonstrated that these relatively immature erythroid cells require erythropoietin in order to maintain their viability and to differentiate into mature erythrocytes (Koury, M. J., et al., J Cell Physiol 121:526-32 (1984); Koury, M. J., et al., Proc Natl Acad Sci USA 79:635-9 (1982); Koury, M. J., et al., J Cell Physiol 126:259-65 (1986); Bondurant, M. C., et al., Mol Cell Biol 5:675-80 (1985); Sawyer, S. T., et al., J Biol Chem 261:9187-95 (1986); Koury, M. J., et al., J Cell Physiol 137:65-74 (1988); Koury, M. J., et al., Blood Cells 13:217-26 (1987); Koury, M. J., et al., J Cell Physiol 133:438-48 (1987)). During differentiation in response to erythropoietin, these cells increase globin gene transcription and synthesis of hemoglobin, transfer and receptor synthesis, and the synthesis of integral erythrocyte membrane proteins. They also undergo other normal differentiation-associated events such as enucleation and extensive membrane rearrangement.

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L10: Entry 14 of 15 File: USPT Nov 11, 1997

DOCUMENT-IDENTIFIER: US 5686436 A
**** See image for Certificate of Correction ****
TITLE: Multi-faceted method to repress reproduction of latent viruses in humans and animals

Detailed Description Text (51):
The embodiments described herein may be employed for treating a wide array of viruses, including retroviruses. Examples of such viuses include, but are not limited to, Abelson murine leukemia virus, Adult T cell leukemia virus, AKR murine leukemia virus, Avian acute leukemia virus, Avian erythroblastosis virus, Avian Influenza virus, Avian leukemia sarcoma virus, Avian leukemia virus, Avian leukosis virus, Avian mycloblastosis virus, Avian sarcoma virus, Arian sarcoma-leukemia virus, Baboon endogenous retrovirus, Bovine immunodeficiency virus, Bovine leukemia virus, Bovine synctial virus, Bovine syncytium forming virus, Caprine arthritis encephalitis virus, Chick synctial virus, Chicken synctial virus, Duck infectious anemia virus, Equine infectious anemia virus, FBJ murine osteogenic murine sarcoma virus, FBJ murine sarcoma virus, Feline immunodeficiency virus, Feline leukemia virus, Feline sarcoma virus, Feline syncytium forming virus, Foamy viruses, Friend murine leukemia virus, Friend spleen focus forming virus, Fujinami sarcoma virus, Gardner--Rasher feline sarcoma virus, Gibbon ape leukemia virus, Gross virus, Hamster synctium forming virus, Hardy-Zuckerman feline sarcoma virus, Harvy murine sarcoma virus, Human immunodeficiency I, Human immunodeficiency II, Human immunodeficiency virus, Human spuma virus, Human T cell leukemia virus, Human T cell leukemia virus type I, Human T cell leukemia virus type II, Human T cell leukemia virus type III, Kirsten murine sarcoma virus, Lentiviruses (general terms), Mason pfizer monkey virus, Mink cell focus forming murine leukemia virus, Mo T cell virus, Moloney murine leukemia virus, Moloney murine sarcoma virus, Mouse mammary tumor virus, Murine parvo virus, Myeloblastosis associated virus, Myelocytomastosis virus 29, Myeloproliferative sarcoma virus, Murine leukemia virus, Murine parvovirus, Oncoviruses, Oregon sockeye salmon disease virus, PO-I-Lu virus, Rabbitpox papilloma virus, Reticuloendotheliosis strain T, Reticuloendotheliosis-associated, Rous sarcoma virus, Sacramento River Chronic Disease (Salmon), Sea lion foamy virus, Simian foamy virus, Simian immunodeficiency, Simian retrovirus type I, Simian retrovirus type II, Simian retrovirus type III, Simian retrovirus type IV, Simian retrovirus type V, Simian sarcoma associated virus, Simian sarcoma virus, Simian T cell leukemia virus, Simian T cell leukemia virus type HI, Simian T lymphoma virus I, Snyder-Thelin feline sarcoma virus, South African ovine macdi-visma virus, Spleen focus forming virus, Spima virus, Spimavirus, Squrrel monkey retrovirus (Aotus), and Spuma-Maedi virus.

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L4: Entry 5 of 32 File: PGPB Sep 4, 2003

DOCUMENT-IDENTIFIER: US 20030167500 A1
TITLE: Methods and compositions for generating a genetically modified animal using lentiviral vectors

Detail Description Paragraph:
[0074] One of skill will recognize that the trans-retroviral vector design can be used in viral vectors derived from any retroviral source. Accordingly, in specific embodiments of the present invention, a trans-retroviral vector is derived from a retrovirus other than a lentivirus. Such retroviral vectors can be derived from, but not limited to, retrovirus, including but not limited to, Moloney Leukemia Virus (MLV), Abelson murine leukemia virus, AKR (endogenous) murine leukemia virus, Avian carcinoma, Mill Hill virus 2, Avian Leukosis virus--RSA, Avian myeloblastosis virus, Avian myelocytomatosis virus 29, Bovine syncytial virus, Caprine arthritis encephalitis virus, Chick syncytial virus, Equine infectious anemia virus, Feline leukemia virus, Feline syncytial virus, Finkel-Biskis-Jinkins murine sarcoma virus, Friend murine leukemia virus, Fujinami sarcoma virus, Gardner-Arnstein feline sarcoma virus, Gibbon ape leukemia virus, Guinea pig type C oncovirus, Hardy-Zuckerman feline sarcoma virus, Harvey murine sarcoma virus, Human foamy virus, Human spumavirus, Human T-lymphotropic virus 1, Human T-lymphototropic virus 2, Jaagsiekte virus, Kirsten murine sarcoma virus, Langur virus, Mason-Pfizer monkey virus, Moloney murine sarcoma virus, Mouse mammary tumor virus, Ovine pulmonary adenocarcinoma virus, Porcine type C oncovirus, Reticuloendotheliosis virus, Rous sarcoma virus, Simian foamy virus, Simian sarcoma virus, Simian T-lymphotropic virus, Simian type D virus 1, Snyder-Theilen feline sarcoma virus, Squirrel monkey retrovirus, Trager duck spleen necrosis virus, UR2 sarcoma virus, Viper retrovirus, Visna/maedi virus, Woolly monkey sarcoma virus, and Y73 sarcoma virus human-, simian-, feline-, and bovine immunodeficiency viruses (HIV, SIV, FIV, BIV). See also, U.S. patent application Ser. No. 09/578,548.

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L4: Entry 6 of 32 File: PGPB Aug 7, 2003

DOCUMENT-IDENTIFIER: US 20030148520 A1
TITLE: Cell-specific adenovirus vectors comprising an internal ribosome entry site

Detail Description Paragraph:
[0129] Recent studies showed that both Friend-murine leukemia virus (MLV) 5'-UTR and rat retrotransposon virus-like 30S (VL30) sequences contain IRES structure of retroviral origin (Torrent et al. (1996) Hum Gene Ther 7:603-612). These fragments are also functional as packing signal when used in retrovirus derived vectors. Studies of avian reticuloendotheliosis virus type A (REV-A) show that its IRES maps downstream of the packaging/dimerization (E/DLS) sequence and the minimal IRES sequence appears to be within a 129 nt fragment (452-580) of the 5' leader, immediately upstream of the gag AUG codon (Lopez-Lastra et al. (1997) Hum Gene Ther 8:1855-1865).

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L4: Entry 13 of 32 File: USPT Mar 9, 2004

DOCUMENT-IDENTIFIER: US 6703226 B1
TITLE: Expression of a foamy virus envelope protein

Brief Summary Text (7):
In a particularly preferred embodiment, the modified FV env protein in use in the present invention is a fusion protein which furthermore comprises all or preferably a part of a non-FV retroviral envelope protein. Examples of suitable non-FV retroviruses include avian retroviruses, bovine retroviruses, feline retroviruses, murine retroviruses such as Murine Leukemia Virus (MuLV) and particularly Moloney MuLV (MoMuLV), Friend Murine Leukemia Virus (FrMuLV) especially strain FB 29, Murine Sarcome Virus (MSV), primate retroviruses such as GaLV, VSV or lentiviruses such as HIV (Human Immunodeficiency Virus) or SIV (Simian Immunodeficiency Virus).

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L4: Entry 17 of 32 File: USPT Sep 17, 2002

DOCUMENT-IDENTIFIER: US 6451304 B1
TITLE: Method for retrovirus vector production by separated gag and pol expression

Detailed Description Text (3):
The MoMLV gag-pol encoding DNA sequence consists of nucleotides 368-58837 of the MoMLV genomic nucleotide sequence (reported in RNA Tumor Viruses, Vol. 11, Cold Spring Harbor Laboratories, 1985; GenBank Accession No. J02255; SEQ.ID.NO. 1). Those of ordinary skill in the art will appreciate that other expressible retroviral polynucleotides (i.e., polynucleotides in operable linkage with regulatory and control sequences, such as promoters, to operably express the encoded retroviral gene) may be used to construct provirus plasmids for use in the invention (preferably from murine or avian retroviruses), such as the murine sarcoma virus (e.g., GenBank No. V01185); Friend murine leukemia virus (e.g., GenBank No. Z 11128); murine osteosarcoma virus (e.g., GenBank No. K02712); other murine type C retroviruses (e.g., GenBank No. X94150); CAS-BR-E murine leukemia virus (e.g., GenBank No. X57540); avian IC10 retrovirus (e.g., GenBank No.13744); rous sarcoma virus (e.g., GenBank No. ALRDA), avian leukosis virus (ALV) and HIV.

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L4: Entry 19 of 32 File: USPT Jun 11, 2002

DOCUMENT-IDENTIFIER: US 6403300 B1
TITLE: Monoclonal antibodies for detection of friend murine leukemia virus

Brief Summary Text (5):
Several monoclonal antibodies which react with the Friend murine leukemia virus (F-MuLV) and related retroviruses have been produced (CHESEBRO, B. et al. (1983a) Virology 127, 134-148). These antibodies have been used to titrate and distinguish a mixture of ecotropic F-MuLV and dual-tropic Friend mink cell focus-inducing (MCF) viruses in a focal infectivity assay (FIA) using indirect membrane immunofluorescence to detect foci of infected live cells (SITBON, M. et al. (1985) Virology 141, 110-118). However, with immunofluorescence microscopy it has often been difficult to find low power (10.times.) objectives with sufficient light gathering capacity to facilitate visualization of foci. Higher magnifications can be used, but this greatly increases the labor of scanning culture wells to count foci of viral infection. These problems can be overcome by using immunoperoxidase, rather than immunofluorescence in the detection of foci, but in this situation it is desirable to carry out tests on methanol-fixed cells both to eliminate endogenous peroxidase and to allow detection of antigens in the cytoplasm of infected cells. Furthermore, the use of fixed cells aids greatly in the convenience of performing assays since multiple assays can be prepared and stored for processing at a later time. However, monoclonal antibodies generated against protein antigens in their native state frequently will not recognize the viral antigens after fixation.

L4: Entry 27 of 32 File: USPT Jan 12, 1999

DOCUMENT-IDENTIFIER: US 5858744 A
TITLE: Retroviral vector hybrids and the use thereof for gene transfer

Brief Summary Text (27):
The advantages according to the invention are exhibited in transient transfections of reporter gene constructs in numerous representative cell lines of humans and mice. It has surprisingly turned out that U3 sequences of mouse retroviruses of the Friend murine leukemia virus (F-MuLV) family in combination with leader sequences (preferably tRNA binding site) of MESV enable an especially efficient gene expression in myeloid stem and precursor cells. The increase of the gene expression with the vector hybrids according to the invention is more than a power of ten compared to MoMUSV. This applies to relatively late precursor cells of the granulocytes, macrophages and erythrocytes as well as to the early multipotent precursors and even stem cells of the myeloid system. The vector hybrids according to the invention enable an efficient gene expression especially in the case of immature multipotent myeloid cells in which MoMuSV-LTR exhibits a pronounced primary silencing. The activity is also high in the lymphatic system as well as in fibroblasts.

Brief Summary Text (48):
A further subject matter of the invention is a replication-defective infectious virus particle which contains a retroviral RNA as the genome wherein the genome contains a leader region from MESV which contains a packaging function and a tRNA binding site, and contains a heterologous gene for the virus which can be expressed in a eukaryotic cell and contains at the 3' end U3 and R from a Friend murine leukemia virus (F-MuLV) but no active gag, env and pol sequences.

Brief Summary Text (50):
A further subject matter of the invention is the use of a replication-defective retroviral vector hybrid according to the invention which contains the leader region of MESV as the leader region and the U3 and R regions from a Friend murine leukemia virus (F-MuLV) as the U3 and R regions in the 3'-LTR for the production of a pharmaceutical agent for ex vivo or in vivo gene therapy.

Brief Summary Text (64):
A further subject matter of the invention are ecotropic, xenotropic, amphotropic or polytropic retroviruses capable of replication containing the regulatory elements (leader region) of MESV and optionally MoMuLV or MoMuSV combined with the U3 and R regions from a Friend murine leukemia virus (F-MuLV) as U3 and R regions in the 3'-LTR, which as a result are capable of more efficiently infecting murine (in vivo and in vitro) or human (in vitro) precursor cells and to trigger mutations. The retroviruses preferably contain the LTR from F-MuLV as the 3'-LTR.

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L4: Entry 27 of 32 File: USPT Jan 12, 1999

US-PAT-NO: 5858744
DOCUMENT-IDENTIFIER: US 5858744 A

TITLE: Retroviral vector hybrids and the use thereof for gene transfer

DATE-ISSUED: January 12, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Baum; Christopher	Hamburg			DE
Stocking-Harbers; Carol	Hamburg			DE
Ostertag; Wolfram	Hamburg			DE

US-CL-CURRENT: 435/456; 435/320.1, 435/366, 435/372, 435/372.1, 435/457

CLAIMS:

We claim:

1. A retroviral vector hybrid comprising

a) a 5'-LTR-comprising at least one U5 region or tRNA primer binding site wherein the region or site is selected from the group consisting of the U5 region of MESV, the tRNA primer binding site of MESV, the U5 region of MoMuSV, and the tRNA primer binding site of MoMuSV, and

b) a 3'-LTR comprising the U3 and R regions from a Friend murine leukaemia virus (F-MuLV).

2. The vector hybrid of claim 1 further comprising the leader region of MESV.

3. The vector hybrid of claim 1, wherein the Friend murine leukaemia virus is selected from the group consisting of malignant histiosarcoma virus (MHSV), SFFVp Lilly-Steeves, SFFVa, Rauscher SSFV, F-muLVc157 and Friend-mink cell focus forming Virus.

4. The vector hybrid of claim 1, wherein the U3 and R regions in the 5'-LTR comprise the U3 and R regions from MPSV, MESV or PCMV.

5. The vector hybrid of claim 1, wherein the 5'-LTR comprises bp 142-657 from SEQ ID NO:1.

6. The vector hybrid of claim 1, wherein the 3'-LTR comprises bp 1707-2283 from SEQ ID NO:1.

7. The vector hybrid of claim 1 further comprising at least one gene that is heterologous to the retroviral vector and can be expressed in eukaryotic cells.

8. The vector hybrid of claim 1 which is replication-defective.

9. The vector hybrid of claim 1 which is replication-competent.

10. The vector hybrid of claim 7 wherein the heterologous gene is selected from the group consisting of a multiple drug resistance gene (MDR gene), an antibiotic resistance gene, a LNGFR gene, a cerebrosidase gene and the herpes simplex TK gene.

11. The vector of claim 10 wherein the heterologous gene is the neo.sup.R gene.

12. A vector hybrid selected from the group consisting of pSF1, pSF2, pSF3, and pHM1.

13. A process for the production of a retrovirally transduced eukaryotic cell which expresses an exogenous gene, said process comprising transducing a eukaryotic cell with a retroviral vector virus, which virus comprises

a) at least one U5 region or tRNA primer binding site wherein the region or site is selected from the group consisting of the U5 region of MESV, the tRNA primer binding site of MESV, the U5 region of MoMuSV, and the tRNA primer binding site of MoMuSV, and

b) a 3'-LTR comprising the U3 and R regions from a Friend murine leukaemia virus (F-MuLV).

14. The process as claimed in claim 13 wherein the retroviral vector virus is replication defective.

15. The process as claimed in claim 13 wherein the eukaryotic cells is a haematopoietic stem cells.

16. An eukaryotic cell obtained by the process of transducing a eukaryotic cell with a retroviral vector virus comprising

a) at least one U5 region or tRNA primer binding site wherein the region or site is selected from the group consisting of the U5 region of MESV, the tRNA primer binding site of MESV, the U5 region of MoMuSV, and the tRNA primer binding site of MoMuSV, and

b) a 3'-LTR comprising the U3 and R regions from a Friend murine leukaemia virus (F-MuLV).

17. The cell of claim 16 wherein the F-MuLV is selected from the group consisting of malignant histiosarcoma virus (MHSV), SFFVp Lilly-Steeves, SFFVa, Rauscher SSFV, F-muLVc157 and Friend-mink cell focus forming virus.

18. The cell of claim 16 wherein the vector further comprises the leader region of MESV.

19. The cell of claim 16 wherein the retroviral vector virus is replication defective.

20. A replication defective infectious virus particle comprising a retroviral RNA genome, wherein the genome comprises

a) at least one U5 region or tRNA primer binding site selected from the group consisting of the U5 region of MESV, the tRNA primer binding site of MESV, the U5 region of MoMuSV, and the

tRNA primer binding site of MoMuSV, and

b) further comprises a packaging function, a gene which is heterologous to the virus and can be expressed in the eukaryotic cell, and U3 and R from a Friend murine leukaemia virus (F-MuLV), but

c) does not comprise active gag, env and pol sequences at the 3' end.

21. A process for the production of a replication defective infectious virus particle comprising

a) transfecting a eukaryotic helper cell which has the helper functions gag, env and pol with a vector hybrid comprising

i) at least one U5 region or tRNA primer binding site wherein the region or site is selected from the group consisting of the U5 region of MESV, the tRNA primer binding site of MESV, the U5 region of MoMuSV, and the tRNA primer binding site of MoMuSV, and

ii) a 3'-LTR comprising the U3 and R regions from a Friend murine leukaemia virus (F-MuLV),

b) producing the RNA corresponding to the DNA of the vector hybrid as the virus genome in the cell,

c) packaging the virus genome into the replication deficient empty virus envelopes formed in the cell, and

d) isolating the infectious virus particles which contain said virus genome.

22. The process of claim 21 wherein the F-MuLV is selected from the group consisting of malignant histiosarcoma virus (MHSV), SFFVp Lilly-Steeves, SFFVa, Rauscher SFFV, F-muLVc 157 and Friend-mink cell focus forming virus.

23. The process of claim 21 wherein the vector hybrid further comprises the leader region of MESV.

24. A retroviral vector hybrid comprising

a) the U5 region and tRNA primer binding site of MESV as the U5 region and the tRNA primer binding site in the leader region, and

b) the U3 and R regions from myeloproliferative sarcoma virus (MPSV) as the U3 and R regions in the 3'-LTR.

25. A process for the production of a retrovirally transduced eukaryotic cell comprising an exogenous gene, wherein the eukaryotic cell is transduced with the retroviral vector virus comprising:

a) the U5 region and/or tRNA primer binding site of MESV as the U5 region and/or tRNA primer binding site in the leader region,

b) the U3 and R regions from myeloproliferative sarcoma virus (MPSV) as the U3 and R regions in the 3'-LTR and

c) the said exogenous gene.

26. A replication defective infectious virus particle comprising retroviral RNA as the genome, wherein the genome comprises the U5 regions and/or tRNA primer binding site of MESV as the U5 region and/or tRNA primer binding site, a packaging function and a gene which is heterologous for the virus and can be expressed in the eukaryotic cell, and U3 and R from the myeloproliferative sarcoma virus (MPSV) but no active gag, env and pol sequences at the 3' end.

(FILE 'HOME' ENTERED AT 17:41:16 ON 24 MAY 2004)

FILE 'MEDLINE, CANCERLIT, EMBASE, BIOTECHDS, CAPLUS, BIOSIS' ENTERED AT 17:41:41 ON 24 MAY 2004

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L1          4156 S FR-MULV OR F-MULV OR FRIEND LEUKEMIA VIR?
L2       2308279 S EXPRESSION VECTOR OR GENE THERAPY OR TRANSFE?
L3           372 S L2 AND L1
L4       1235774 S EXOGENOUS OR HETEROLOGOUS OR REPORTER OR GALACTOSIDASE OR MAR
L5            37 S L4 AND L3
L6            22 DUP REM L5 (15 DUPLICATES REMOVED)
L7            34 S ISOLATED AND L3
L8            16 DUP REM L7 (18 DUPLICATES REMOVED)
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L6 ANSWER 21 OF 22 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1978:167001 BIOSIS
DN PREV197865054001; BA65:54001
TI IMMUNO THERAPY OF MURINE LEUKEMIA PART 1 PROTECTION AGAINST **FRIEND LEUKEMIA VIRUS** INDUCED DISEASE BY PASSIVE SERUM THERAPY.
AU COLLINS J J [Reprint author]; SANFILIPPO F; TSONG-CHOU L; ISHIZAKI R; METZGAR R S
CS DEP SURG, DUKE UNIV MED CENT, DURHAM, NC 27710, USA
SO International Journal of Cancer, (1978) Vol. 21, No. 1, pp. 51-61.
CODEN: IJCNAW. ISSN: 0020-7136.
DT Article
FS BA
LA ENGLISH
AB Passive serum therapy with chimpanzee antiserum raised against **Friend leukemia virus** (FLV) or the major viral envelope glycoprotein of FLV, gp71, was effective in protecting mice against the development of virus-induced disease. The **heterologous** serum was administered in 4 doses beginning 3 days after virus inoculation and the mice were followed for the development of splenomegaly, virus level and the induction of a host antiviral immune response. The latter was measured by an in vitro humoral cytotoxicity assay using FLV-releasing mouse cells as targets, as well as direct radioimmunoassay for the presence of mouse antibodies capable of binding FLV gp71. The results indicate a close correlation between the development of antiviral humoral immunity and protection against splenomegaly, with both of these parameters being inversely related to serum and spleen infectious virus titers. Recognition of and response to the administered **heterologous** immunoglobulin in by the recipient animal does not appear to represent an integral part of the mechanism leading to protection, as determined by the absence of mouse antibodies capable of binding chimpanzee γ-globulin, as well as by the equal efficacy of the passive serum **transfer** protocol in mice after induction of tolerance to chimpanzee γ-globulin. Passive serum therapy protection may function via a mechanism involving the reduction of the virus burden below a level which is immunosuppressive, allowing the development of a host antiviral immune response which is necessary for elimination of virus and/or infected cells leading to long-term resistance.

L6 ANSWER 17 OF 22 MEDLINE on STN DUPLICATE 6
AN 86243659 MEDLINE
DN PubMed ID: 3719096
TI Long-term culture of bone marrow-derived preleukemic cells from **F**-**MuLV**-infected mice.
AU Heard J M; Sola B; Martial M A; Fichelson S; Gisselbrecht S
SO Blood, (1986 Jul) 68 (1) 193-9.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198607
ED Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19860730
AB The replication-competent **Friend leukemia virus** (**F-MuLV**) induces leukemias involving three hematopoietic lineages after a latent period of several months. In an attempt to elucidate the early events of the leukemogenic process, we looked for a method allowing the isolation and the long term in vitro maintenance of preleukemic cells. When established as long-term cultures according to the technique described by Dexter et al, bone marrow cells obtained from 7/7 apparently healthy **F-MuLV**-infected preleukemic mice led to the accumulation of immature myeloblastic cells, and to the generation of permanent myeloblastic cell lines, which in most cases further became tumorigenic in preirradiated recipient animals. The delays required to obtain cell lines were shorter when the duration of the in vivo infection was longer, suggesting that these cells were committed into the leukemogenic pathway before their **transfer** into culture flasks. The myelomonocytic preleukemic cells exhibited normal sensitivity to purified preparations of CSFs, but acquired the capacity to grow in the absence of **exogenous** CSF stimulation. Examination of integrated provirus copies demonstrated that the preleukemic cell proliferation involved a single or a few clones which may progress in vitro from a preleukemic to a fully malignant stage without major modifications of the integrated provirus copies.

L6 ANSWER 12 OF 22 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
AN 1995-01562 BIOTECHDS
TI A retro viral vector derived from **Fr-MuLV** with high infection efficacy;
mouse Friend virus vector production for use in **gene therapy** (conference abstract)
AU Cohen-Haguenauer O; Restrepo L M; Dumey N; Masset M; Heard J M; Marty M
CS Inst.Hematol.Paris; St.Louis-Hosp.Paris; Inst.Pasteur-Paris
LO Gene Transfer and Molecular Oncology, Institute of Haematology, 75475 Paris Cedex 10, France.
SO Gene Ther.; (1994) 1, Suppl.2, S11
CODEN: 4352W
Second Meeting of the European Working Group on Human Gene Transfer and Therapy, London, UK, 18-21 November, 1994.
DT Journal
LA English
AB Retro virus vectors based on strains selected for both tropism in animals and high infectivity were developed. A mouse **Friend-leukemia virus** (**Fr-MuLV**) FB29 vector was constructed, with or with a splice acceptor (splice vector), using a Neo **reporter** gene and long terminal repeat (LTR). High-producing clones were selected after **transfection** of a Psi-CRIP amphotropic packaging cell culture. An **Fr-MuLV** vector without splice acceptor sequences showed highest infectivity on NIH3T3 cells. A producer clone was selected with more than 1 copy vector transduction into target cells and viral titers of over 10 million cfu/ml. Defective retro virus integration sites were studied in Vero and human primary fibroblast cells. The vector were evaluated on a wide range of human and mouse cells, including glial and Schwann cell lines, human T-lymphocytes, K562 and U937 cells. A 2nd self-inactivating construct was designed with inactivation of the U3 enhancer in the 3'-end LTR, to increase safety and provide an internal promoter. An epidermal growth factor gene was cloned and the construct was evaluated in mouse and human epithelium cells. (0 ref)

L6 ANSWER 11 OF 22 CANCERLIT on STN
AN 95612727 CANCERLIT
DN 95612727
TI A retroviral vector derived from **Fr-MuLV** with high infection efficacy (Meeting abstract).
AU Cohen-Haguenauer O; Restrepo L M; Dumey N; Massett M; Heard J M; Marty M
CS Inst. of Hematology, Pasteur Inst., 75475 Paris, France.
SO Gene Ther, (1994) 1 (Suppl 2) S11.
ISSN: 0969-7128.
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Institute for Cell and Developmental Biology
EM 199510
ED Entered STN: 19951012
Last Updated on STN: 19970509
AB Only significant technological improvements in terms of tools for gene **transfer**, efficacy and safety will allow for therapeutic improvement of patients conditions using gene **transfer** and therapy approaches. We have thus been focusing our efforts on the design of original retroviral vectors based on viral strains which have been selected according to both tropism in the animals and high infectivity with special attention to Friend-MuLV (**Fr-MuLV**) FB29-strain. Several constructs have been derived either including a splice acceptor (splice vector) or not. Initial evaluation has been performed with the NeoR gene as **reporter** and LTRs driven transcription. High producing clones have been selected following **transfection** into Psi-CRIP amphotropic packaging cell line. A construct derived from **Fr-MuLV** devoid of splice acceptor sequences has demonstrated highest infection efficacy onto NIH3T3 cells. A producer clone has been selected which is likely to show more than one copy vector transduction into target cells on southern blots; together with viral titers over 10(7) cfu/ml. This lead us to explore defective retrovirus vector integration sites in cells of primate non-human (Vero cells) or human (primary fibroblasts) origin. Amplification onto 3T3 cells followed by check for absence of generation of NeoR clones onto secondary 3T3 cells and repeated helper virus mobilization assays onto 3T3BAG cells have remained negative. Viral supernatant has been injected intraperitoneally into newborn mice without resulting transforming activity to this date (9 months follow-up). The infection spectrum and potential of this vector has been evaluated on a wide range of target cells of human or murine origin (joined abstract for hemopoietic progenitors); including glial cells and Schwann cell lines where sustained LTR-driven expression of the transgene could be evidenced for several months; human T-cell lines (Jurkatt and Y2TC2) together with K562 (erythromega) and U937 (mono-macro) have also been successfully infected as evidenced by in vitro cultures of several weeks in the presence of G418 selection and 3H-thymidine incorporation. A second virus construct has been designed including an inactivation of the U3-enhancer in the 3' end LTR (self-inactivating retro-viral vector) through a deletion of the major part of the U3 region sparing the TATA-box but not the CAAT-box; in order to both increase safety and derive constructs including internal promotor specifying the transcription. The R-EGF has been cloned and the construct is currently being evaluated on cells of epithelial origin whether murine or human.

currently underway.

L6 ANSWER 8 OF 22 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
AN 1994-11042 BIOTECHDS
TI An original retroviral vector derived from **Fr-MuLV** with high infection efficacy;
Friend-Moloney leukemia virus retro virus vector construction and characterization, and potential application in **gene therapy** (conference abstract)
AU Cohen-Haguenauer O; Restrepo L M; Heard J M; Marty M; Boiron M
CS Inst.Hematol.Paris; Inst.Pasteur-Paris
LO Lab. Transfert Genetique et Oncologie Moleculaire, Institut d'Hematologie, Hopital Saint Louis, Paris, France.
SO Cancer Gene Ther.; (1994) 1, 2, 141
CODEN: 2815V
DT Journal
LA English
AB Several retro virus vectors were designed based on Friend-Moloney leukemia virus (**Fr-MuLV**) FB29 and on cat sarcoma virus Sm. Initial evaluations were performed using the neomycin-resistance (Nr) **reporter** gene. Nr producer clones were derived following **transfection** into Psi-CRIP amphotropic packaging cell line. High producing clones were selected using a polymerase chain reaction followed by Southern blot analysis to determine transgene average copy number into infected mouse NIH3T3 fibroblasts target cells. Standard dilutions of the virus supernatant were used to perform titration assays to characterize the multiplicity of infection. A construct derived from **Fr-MuLV** devoid of splice acceptor sequences demonstrated the highest infection efficacy into NIH3T3 cells. Several clones were selected which showed one-copy vector transduction into target cells. The infection spectrum and potential of various constructs derived from this vector were being evaluated. A wide range of target cells of human origin were submitted to infection, with specific attention of hematopoietic stem cells. (0 ref)

L8 ANSWER 10 OF 16 MEDLINE on STN DUPLICATE 4
AN 80163023 MEDLINE
DN PubMed ID: 6245244
TI **Transfection** of molecularly cloned Friend murine leukemia virus DNA yields a highly leukemogenic helper-independent type C virus.
AU Oliff A I; Hager G L; Chang E H; Scolnick E M; Chan H W; Lowy D R
SO Journal of virology, (1980 Jan) 33 (1) 475-86.
Journal code: 0113724. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198006
ED Entered STN: 19900315
Last Updated on STN: 19970203
Entered Medline: 19800625
AB Unintegrated viral DNA was **isolated** via the Hirt procedure from mouse fibroblasts newly infected with Friend murine leukemia virus (**F-MuLV**) clone 201, a biologically cloned helper virus **isolated** from stocks of **F-MuLV** complex. A physical map of the unintegrated in vivo linear viral DNA was generated for several restriction endonucleases. The supercoiled viral DNA was digested with EcoRI, which cleaved the viral DNA at a unique site. The linearized viral DNA was then inserted into lambda gtWES.lambda B at the EcoRI site and cloned in an approved EK2 host. Eight independent lambda-mouse recombinants were identified as containing **F-MuLV** DNA inserts by hybridization with **F-MuLV** 32P-labeled complementary DNA. One of the **F-MuLV** DNA inserts was 9.1 kilobases (kb) and had the same restriction enzyme sites as the unintegrated linear **F-MuLV** DNA. Six inserts were 8.5 kb; each lacked a single copy of the terminally redundant sequences of the unintegrated linear viral DNA. One insert was 8.2 kb and contained a 0.9-kb deletion. After digestion with EcoRI, one recombinant DNA preparation containing an 8.5-kb insert was infectious for NIH 3T3 cells. Undigested recombinant DNA was not infectious. The infectivity of the EcoRI-digested DNA followed multihit kinetics, indicating that more than one molecule was required to register as an infectious unit. The virus **isolated** from this **transfection** (**F-MuLV**-57) was NB-ecotropic, helper-independent, and formed XC plaques. Inoculation of this virus into newborn NIH Swiss mice induced leukemia and splenomegaly in greater than 90% of animals within 3 to 4 weeks. The gross and microscopic abnormalities induced by **F-MuLV** clone 57 were identical to those seen with the original parent stocks of **F-MuLV** clone 201. These results indicate that this helper-independent **F-MuLV** can induce a rapid nonthymic leukemia in the absence of the spleen focus-forming virus.